

Improve your skills and knowledge in epileptology

NEW virtual
campus and
online learning
environment



Work on your
competencies

Explore the
course portfolio

Track your
progress

Earn a certificate

The International League Against Epilepsy (ILAE) introduces highly interactive, practice-oriented online courses for healthcare professionals worldwide who diagnose and treat epilepsy.

The ILAE Academy offers:








- Competency-based e-learning for different levels of expertise¹
- Content developed by ILAE experts
- Realistic cases covering most common epilepsies



**EXPLORE
AND REGISTER**
www.ilae-academy.org

1. Blümcke, Ingmar, et al. "Roadmap for a competency-based educational curriculum in epileptology: report of the Epilepsy Education Task Force of the International League Against Epilepsy." *Epileptic Disorders* 21.2 (2019): 129-140.

A new era in electroencephalographic monitoring? Subscalp devices for ultra-long-term recordings

Jonas Duun-Henriksen^{1,2}  | Maxime Baud^{3,4}  | Mark P. Richardson¹  |
Mark Cook^{5,6}  | George Kouvas⁴ | John M. Heasman⁷ | Daniel Friedman⁸  |
Jukka Peltola⁹ | Ivan C. Zibrandtsen¹⁰  | Troels W. Kjaer^{10,11} 

¹Department of Basic & Clinical Neuroscience, King's College London, London, UK

²UNEEG medical, Lyngby, Denmark

³Sleep-Wake-Epilepsy Center and Center for Experimental Neurology, Department of Neurology, Bern University Hospital, University of Bern, Bern, Switzerland

⁴Wyss Center for Bio and Neuroengineering, Geneva, Switzerland

⁵Graeme Clark Institute, University of Melbourne, Melbourne, Victoria, Australia

⁶Epi-Minder, Melbourne, Victoria, Australia

⁷Cochlear, Sydney, New South Wales, Australia

⁸NYU Langone Comprehensive Epilepsy Center, New York, New York, USA

⁹Department of Neurology, Tampere University and Tampere University Hospital, Tampere, Finland

¹⁰Center of Neurophysiology, Department of Neurology, Zealand University Hospital, Roskilde, Denmark

¹¹Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Correspondence

Jonas Duun-Henriksen, UNEEG Medical
A/S, Nymøllevej 6, 3540 Lyngby, Denmark.
Email: jonas.duun-henriksen@kcl.ac.uk

Funding information

NH&MRC; Region Southern Denmark;
Engineering and Physical Sciences
Research Council; South London and
Maudsley NHS Foundation Trust;
Innovationsfonden; Health Science
Foundations of Region Zealand; Epilepsy
Foundation

Abstract

Inaccurate subjective seizure counting poses treatment and diagnostic challenges and thus suboptimal quality in epilepsy management. The limitations of existing hospital- and home-based monitoring solutions are motivating the development of minimally invasive, subscalp, implantable electroencephalography (EEG) systems with accompanying cloud-based software. This new generation of ultra-long-term brain monitoring systems is setting expectations for a sea change in the field of clinical epilepsy. From definitive diagnoses and reliable seizure logs to treatment optimization and presurgical seizure foci localization, the clinical need for continuous monitoring of brain electrophysiological activity in epilepsy patients is evident. This paper presents the converging solutions developed independently by researchers and organizations working at the forefront of next generation EEG monitoring. The immediate value of these devices is discussed as well as the potential drivers and hurdles to adoption. Additionally, this paper discusses what the expected value of ultra-long-term EEG data might be in the future with respect to alarms for especially focal seizures, seizure forecasting, and treatment personalization.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2020 The Authors. *Epilepsia* published by Wiley Periodicals LLC on behalf of International League Against Epilepsy

KEYWORDS

automatic seizure detection, chronotherapy, circadian rhythm, epilepsy monitoring and recording, subcutaneous EEG

1 | INTRODUCTION

The average accuracy of seizure diaries is <50%, and this complicates diagnosis and management of epilepsy.^{1,2} Recent progress in the development of wearable electroencephalography (EEG)^{3–6} and non-EEG seizure detection devices was reviewed in a number of papers,^{3,7–10} all revealing the unmet need for devices that could chronically monitor epileptic brain activity. Implantable subscalp EEG devices meet this need by detecting electrographic seizures, which has been shown to be a robust objective measure that correlates to clinical symptoms.^{11,12} In cardiology, the invention of Holter electrocardiography (ECG) and the implantable loop recorder provided a solution for the problem of monitoring rare cardiac events.^{13,14} We anticipate a similar advance in neurology with respect to long-term monitoring of brain activity in epilepsy.

Currently, scalp EEG has several critical limitations for long-term monitoring. Electrodes must be held fixed to the skin either with a cap or an adhesive, such as collodion, and the skin-electrode interface must be maintained regularly to provide good recording quality. Despite intense research on dry-electrode technology, the quality attained so far is not sufficient to warrant broad applicability. Moreover, scalp electrodes are generally acceptable for periods of up to 1–2 weeks at most, which might be insufficient if seizures are infrequent, and surveys show that esthetic appearance is an important variable to determine patients' choice of a method for ambulatory monitoring.¹⁵

Two commercially available intracranial devices enable chronic EEG monitoring. The RNS System (NeuroPace) continuously records counts of epileptic events per hour bin and provides neurostimulation. However, only snippets of raw data can be extracted, amounting to several minutes per 24 hours of monitoring. Percept PC (Medtronic) provides neurostimulation treatment for symptoms associated with movement disorders and obsessive-compulsive disorder as well as epilepsy, where BrainSense technology can also provide a limited form of EEG monitoring (manually triggered 30-second EEG storage and bandpass average power every 10 minutes). However, these are invasive intracranial systems with a clear emphasis on therapeutic neurostimulation rather than diagnostics.

With this gap in mind, a handful of researchers and organizations have individually pioneered the development of subscalp EEG recording devices, reaching converging

Key Points

- A new generation of subscalp, continuous brain monitoring systems have the potential to advance treatment and diagnosis in epilepsy
- First studies comparing subscalp recordings with scalp EEG are favorable and show that seizures can be documented electrographically
- Adoption of subscalp, ultra-long-term EEG monitoring may cause a shift from subjective seizure reporting to objective seizure counting
- The true value of ultra-long-term EEG has yet to be proven; more data collected over long periods of time are essential to show the benefit

technical solutions in recent years, and are currently working on translating the invention to the clinic and market. One subscalp device has recently been launched in Europe (24/7 EEG SubQ, UNEEG Medical), and more are in development at centers and companies around the world. In providing previously unobtainable data, these minimally invasive solutions may lead to a paradigm shift in the management of epilepsy, where clinical decisions will be based on objective brain epileptic activity, including seizure counts, sleep quality, and vigilance.

This review describes the novel class of subscalp EEG recording devices that can be implanted subcutaneously between the scalp and the cranium. A search on PubMed in May 2020 for (((subcutaneous OR subgaleal OR subdermal OR subscalp OR epicranial OR epiosteal) AND EEG) AND (epilepsy OR seizure)) resulted in 116 results, with only a few of the systems mentioned in the current article appearing. Given the sparse literature, we chose to perform a knowledge-driven review of these EEG devices. The review is based on information obtained from literature, conferences, and personal correspondence as well as manually reviewing references to articles mentioned in the literature of the non-EEG and wearable EEG seizure detection devices mentioned above.

We describe and provide an overview of current efforts for subscalp EEG systems, commercially available or in development, and discuss the utility of ultra-long-term monitoring using subscalp devices in epilepsy and the advantages that objective seizure counts can provide. We also speculate on

TABLE 1 Overview and core characteristics of known subscalp EEG systems certified or currently in development

Device	Channels/montage	Recording modalities	EEG sampling rate	Battery	Wearable companion	Continuous raw data available	Status
CE-approved devices							
24/7 EEG SubQ	2 channels/unilateral	EEG + 3 axis accelerometry	207 Hz	External/24 h rechargeable	Yes	Yes	CE-marked by April 2019
Devices in validation phase							
Minder	2 channels/bilateral	EEG	^a	External/24 h rechargeable	Yes	Yes	Clinical trial is ongoing
EASSEE	4 channel/unilateral Laplacian	EEG	^a	^a	Yes	^a	Clinical trial is ongoing
Epios	7 channels/temporal OR 14 channels/bitemporal OR 28 channels/full montage	EEG + ECG + audio + 3 axis accelerometer	250 Hz	External/24 h rechargeable	Yes	Yes	Clinical trial to start in 2020
Neuroview Technology	1 or 2 channels/unilateral	EEG + 3 axis accelerometry	256	Internal/1 y	No	No; only relevant epochs	Clinical trial to start in 2020
UltimateEEG	Up to 8 channels/unilateral	^a	^a	^a	^a	^a	Clinical trial to start in 2020

Abbreviation: EEG, electroencephalography.

^aTo be decided or not yet disclosed.

future possibilities of mechanistic insights into the epileptic brain, seizure forecasting, and combination with non-EEG modalities, and finally, we discuss current challenges and limitations of the subscalp technology.

2 | SUBSCALP EEG AS A NEW MODALITY

EEG is the most important paraclinical modality in diagnosing epilepsy. In addition, it helps classify seizure types and epilepsy syndromes.¹⁶ When routine outpatient EEG provides insufficient information, long-term monitoring in a hospital-based epilepsy monitoring unit (EMU) is the next classical option. To mitigate the high costs of such inpatient investigations, many home-based solutions have been proposed, often involving a few days of scalp EEG and a webcam placed in the patient's house.^{17,18} Depending on the results of these investigations, surgical resection of the seizure focus may be an option, and an additional intracranial EEG study is often required.¹⁹

2.1 | Motivation for subscalp EEG

The development of subscalp EEG devices is motivated by an unmet clinical need that neither scalp nor intracranial EEG addresses: ultra-long-term (ie, >1 month) EEG data collection in a home environment that can reveal temporal fluctuations in patterns of seizures. This may have many advantages for personalized epilepsy management in the context of rare seizures, cycles of epileptic brain activity in a majority of patients, and alternating seizure localization in some individuals with multifocal epilepsies (eg, bitemporal epilepsy).^{20–24} Before discussing its potential for clinical practice in detail in Section 3, a technical review of current solutions for subscalp EEG follows.

2.2 | Key technical aspects

Technically, the electrodes are implanted subcutaneously under the scalp but above the bone. Electrode location differs among devices and can be varied for some. The subscalp placement removes the need for electrode care, avoids skin abrasions, and secures a stable and low-impedance recording, where several types of artifacts are attenuated.^{25–27} Modeling studies show that subscalp electrodes provide more specific and accurate measurements compared to scalp electrodes but with lower spatial and temporal resolution than intracranial electrodes.²⁸ A comparison between subscalp and scalp electrodes shows that the signal quality of the subscalp electrodes were at least equally good during background activity

with closed and open eyes, and might be better during bodily movements.²⁹ Sleep recordings are also improved because subscalp electrodes are less obtrusive than scalp electrodes in the recumbent (sleeping) position. Many algorithms have been proposed to remove noise from EEG³⁰; however, especially for the modalities with only a few channels, this will be challenging although not entirely impossible.³¹

Besides the implant, an external unit for power, data storage, and transmission is needed. Five of six solutions have opted for transmission of the data out of the implant (see below). This requires an external battery that is simple to recharge, easy to use, discreet, and unobtrusive. The system should be able to function for prolonged monitoring for >30 days and potentially for many months or years. Such devices should also be connected to a secure, cloud-based database supported by software applications to help organize and analyze the recorded data. The same five solutions that opted for external battery also provide continuous raw EEG signals for later expert interpretation aided by detection algorithms. Some solutions also include embedded software for real-time EEG analysis, and some solutions are aiming to enhance classification accuracy with multimodal detection algorithms by including other physiological modalities such as ECG, accelerometry, or voice recordings. Table 1 gives an overview of the different current subscalp EEG systems that are described below.

2.3 | Overview of current subscalp EEG systems

Different subscalp devices are proposed, and they vary with respect to the number of channels (from two to 32), degree of invasiveness (one incision under local anesthesia or up to four incisions under local or general anesthesia), and main application (seizure counting, alarming, forecasting, localization, neurofeedback, or neurostimulation). This section provides an overview of the characteristics of different subscalp EEG devices that are presented below in alphabetical order. Figure 1 gives an overview of several of the systems described below as well as main application areas.

24/7 EEG SubQ from UNEEG Medical (Lynge, Denmark) features two bipolar channels introduced under local anesthesia. The SubQ was used to record EEG in healthy subjects²⁹ as well as to detect clinically relevant electrographic seizures in epilepsy patients, showing high reliability and tolerance.^{32,33} The device comes with dedicated software for automatic seizure detection and EEG visualization. The device is CE-marked, and multiple clinical trials are ongoing.³⁴

The Epicranial Application of Stimulation Electrodes for Epilepsy from Precisis (Heidelberg, Germany) uses five subscalp platelet electrodes (four smaller electrodes arranged around a larger center one). This arrangement is inspired

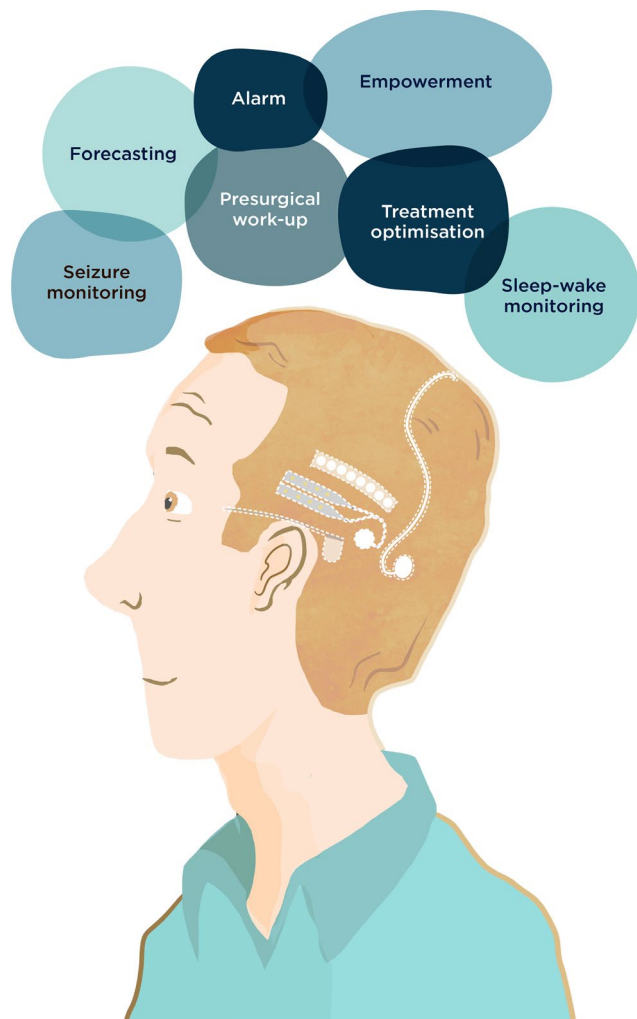


FIGURE 1 Overview of different implantable parts of subscalp devices as well as application areas. From lower left and up: 24/7 EEG SubQ from UNEEG medical, Denmark; the Epios system from the Wyss Center for Bio and Neuroengineering, Switzerland; UltimateEEG from BrainCare Oy, Finland; Minder from Epi-Minder, Australia

by the surface Laplacian concept for improved stimulation depth. It is meant to be implanted above a lesioned brain area and/or epileptogenic focus and is capable of recording as well as delivering neurostimulation at an individualized closed-loop setting.³⁵ A clinical trial is ongoing.

The Epios system from the Wyss Center for Bio and Neuroengineering (Geneva, Switzerland) aims to offer flexible configurations, from focal or bitemporal electrode layouts to broad coverage transposing the locations of the full 10-20 scalp EEG montage to the subscalp compartment. Implantation of the full montage is done under general anesthesia in <1 hour, through two to four small incisions (<1 cm) using specialized epiosteal tunneling tools. With lower coverage, implantation under mild sedation or nerve blocking is being considered. EEG data are transferred wirelessly to a headpiece and on to a body-worn unit for power

and temporary storage.³⁶ The body-worn unit also supports multimodal coregistration (ECG, audio, accelerometry) that is then transmitted to a secure cloud-based application developed to support long-term data visualization and analysis. Preclinical trials are currently ongoing with the Epios implant, and a clinical trial is expected to start in 2020.

Minder from Epi-Minder (Melbourne, Australia) is a subscalp device that implants a multichannel electrode lead across the skull using a tunneling procedure so that both hemispheres are covered. Minder has the potential to provide long-term and continuous measures of the EEG, which will provide a platform to support improved diagnosis and management of epilepsy. A clinical trial is ongoing.

The Neuroview Technology Ally (Englewood, NJ) is being developed as a fully implantable, subscalp EEG recording system to quantify seizures and aid in the diagnosis of infrequent paroxysmal episodes of altered consciousness or convulsive activity.³⁷ The fully implanted device can record for 1 year of continuous use without the need to recharge. Low-power, on-board algorithms identify epochs of subscalp EEG activity suspicious for seizures and patient-identified events. EEG epochs are transferred to a cloud platform via a connected smartphone-based application for the neurologist to review with the aid of cloud-based machine learning algorithms to verify seizures and display and quantify seizure activity between clinic visits. On-device detection algorithms can subsequently be customized to improve the specificity of seizure detection. Clinical trials are expected to commence in 2020.

UltimateEEG from BrainCare Oy (Tampere, Finland) uses platinum on silicon electrodes, with custom order sizes, number of channels, and distance between electrodes. With support for up to eight channels, the device offers mapping of seizure propagation. The planar electrodes are directionally focused toward the electrical sources to reduce electromyographic (EMG) noise. A clinical trial is expected to commence in 2020.

2.4 | Other subscalp EEG systems

Several studies have helped clarify other aspects of subscalp EEG recordings, but none of these seems to have evolved into a commercial concept. Jochum et al³⁸ experimented with an implanted EEG system on a sheep and found a correlation coefficient of 0.86-0.92 with simultaneous scalp EEG at the same location. Ahmed et al³⁹ investigated high-density subdermal EEG probes subjected to artificial aging, compared volume conduction simulations based on four-layered head models, and found that recordings from the subdermal electrodes were less attenuated at higher frequencies than scalp EEG recordings. Do Valle et al⁴⁰ investigated an eight-channel implanted EEG-recorder with electrode arrays projecting

cranially in a fanlike pattern from behind the ear and used it to test a seizure detection algorithm. Xu et al⁴¹ did a proof-of-concept of subscalp EEG sensors that were comparatively insensitive to motion-related artifacts that can be expected to occur more often in daily life. In an intensive care unit setting, low-maintenance subdermal wire electrodes have been used, but although they are quick to set up, they can also be dislodged easily, thus require additional fixation, and do not appear to be practical for chronic monitoring in daily life.²⁷

2.5 | Other modalities

Multimodal monitoring, combining measurements of two or more different modalities, can be used to improve classification accuracy above what can be achieved by using one modality.^{10,42} Heart rate variability features are correlated with para- and sympathetic activity, and this can be used to detect focal seizures or added to EEG-based detection to improve accuracy.⁴² Electrodermal activity exhibits changes during generalized tonic-clonic seizures (GTCS) and focal seizures⁴³ and is positively correlated with longer duration of postictal EEG suppression.⁴⁴ Audio recording could be useful to detect the initial vocalization or noise sometimes occurring during a seizure (ictal cries) or noise that can be characteristic of the postictal period.

Home video combined with ambulatory EEG has demonstrated clinical utility, aiding in interpretation in 14 of 17 (82%) cases in one study.¹⁷ Subscalp EEG recordings could be combined with video or other modalities in a similar way. Video quality in a home setting can be at the same level as in-hospital video recordings, and a majority of patients would prefer home monitoring. Cognitive and behavioral testing during seizures matter for seizure classification and could possibly be implemented in the home setting if online seizure detection algorithms are sufficiently accurate, with low latency of detection after onset. Standardized ictal test batteries have been proposed and are feasible for all but very short seizures.⁴⁵

2.6 | Tolerance and safety

A review of the literature on complication rates with similar devices for deep brain neurostimulation and occipital nerve stimulation revealed that expected complications include infections (<2%), lead migration (~20%), fracture (~4%), and skin erosion (~4%).^{46–49} Infections, a dreaded complication with intracranial material, would here be limited to the subscalp compartment, as the skull would act as an additional protective barrier for the brain. Subscalp hematoma and scalp fibrosis are expected to be very rare.

Prospective tolerance and safety data specific to subscalp EEG come from a single trial.³³ No serious adverse

device-related events occurred, and the patients generally found the device easy to use, although this was only collected anecdotally. Minor annoyances were reported, such as difficulty with simultaneously wearing glasses, occasional nightly disconnections, and the necessity of wearing clothes at night to fix the external device. No participants felt constrained in their ability to perform jobs or leisure activities, although six of nine reported mild headache up to 1 week after surgery. One participant reported uncommon mild headaches that were tolerated without analgesics or other interventions.

In a study with a subdermal wire electrode partially implanted for 60 days in the intensive care unit, no safety concerns were noted.⁵⁰

3 | UTILITY OF SUBSCALP EEG RECORDING

It is estimated that 50% of seizures are unreported, particularly nocturnal seizures or focal seizures with impaired awareness.² The direct consequence is the inability to ascertain therapeutic response; how often is epilepsy undertreated when seizures are underreported, and are true changes in seizure frequency overlooked? Patients may also misclassify nonepileptic events as seizures in their diaries, potentially causing overtreatment. Furthermore, the issue of comorbid epileptic seizures and nonepileptic seizures is not uncommon.⁵¹ In this section, we outline the most important aspects and discuss the practical utility of subscalp EEG.

3.1 | The value of personal long data

Today, there is an ongoing debate on the importance of detecting purely EEG seizures that patients are unaware of and do not feel negatively affected by.⁵² This discussion is important for subscalp EEG, as its ambulatory nature makes simultaneous video unviable and thus difficult to classify seizures as clinical or not. Neuroimaging studies in patients with temporal lobe epilepsy have identified widespread anatomical abnormalities,⁵³ and longitudinal studies in patients with chronic epilepsy show declines in memory and intelligence quotient,⁵⁴ so it is possible that repeated seizures have negative consequences, or perhaps these results come from preferential sampling of the most severely affected patients with chronic refractory epilepsy. In either case, ultra-long-term monitoring technology will be useful in clarifying this important question.

3.2 | The challenge of personal long data

With limited resources available for data review, a prerequisite for ultra-long-term EEG systems is algorithms for

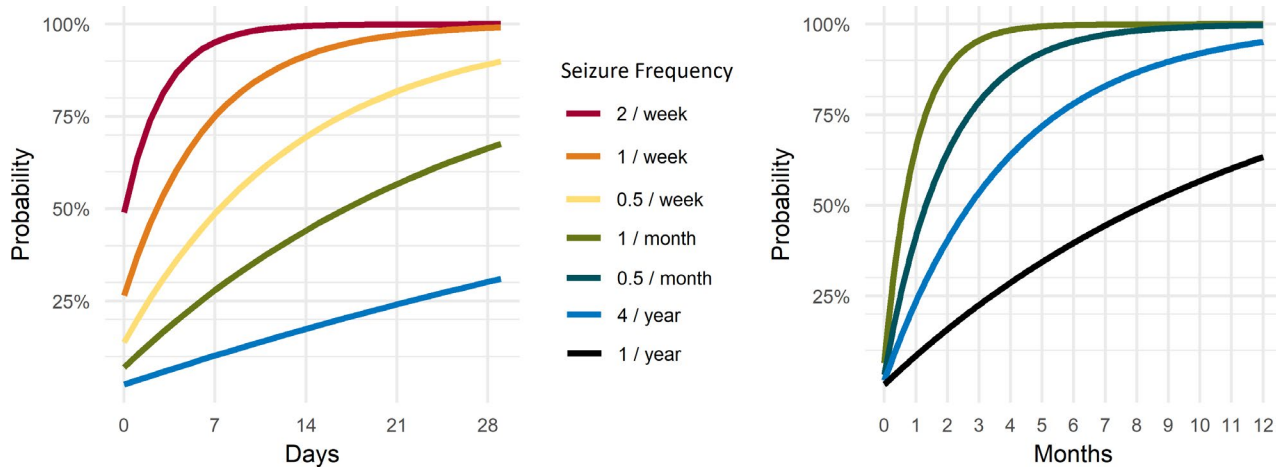


FIGURE 2 Cumulative probability functions for seizure detection as a function of monitoring duration

analysis of the vast amount of recorded data. A trained EEG technician can analyze 24 hours of two-channel EEG in 2-3 hours. Use of trending tools alone can reduce the time for analysis by a factor of 8-10. Whether the algorithms need to be online or offline, simple or complex, and patient-specific or generic will very much depend on the application. The actual time series will always be valuable to validate the findings of the algorithms such that algorithms might be considered a data reduction method, while the final validation is still made by expert EEG reviewers supported by the algorithms. The right level of sensitivity must minimize the number of false negatives, because going through a tractable number of false-positive clips is highly feasible in daily clinical routine. In addition to underlying algorithms, data visualization is also an important issue; if a patient has worn the system for 6 months, a way to obtain an overview of the seizure frequency, seizure duration, periodicity, and time of day would be crucial. With machine learning and big data analysis, the prospects for automated detections are considerable.

3.3 | Objective seizure counting

Treatment decisions are informed by seizure counts, and there have long been calls for more reliable measures than what seizure diaries provide.^{1,2,55,56} Although wearables for the detection of tonic-clonic seizures in particular are gaining approval, the ability to automatically detect focal seizures, particularly with impaired awareness or without major motor features, remains unmet.⁵⁷ Objective seizure counts may inform clinical decisions to avoid that an effective treatment is abandoned because no discernible effect in self-reported measures was apparent⁵⁸ or that an inefficacious treatment is maintained or initiated on the basis of nonepileptic events, because nonseizure events (eg, antiepileptic drug [AED] side effects, nonepileptic seizures) are incorrectly classified as seizures by the patient.

Ultra-long-term EEG data have identified periodic patterns in seizure and spike occurrences operating on different timescales.²² Importantly, cycles appear to be stable within individuals and thus potentially constitute interesting targets for therapeutic intervention.^{22,59}

3.4 | Initial epilepsy diagnosis

The differential diagnosis of epilepsy is broad; syncope and nonepileptic seizures are commonly misdiagnosed as epilepsy, and less commonly, hypoglycemia, paroxysmal disorders of movement, sleep disorders, transient ischemic attack, migraines with aura, and transitory global amnesia.⁵¹ On top of that, there is also the risk of not being diagnosed with epilepsy when recurring seizures are present but not identified. Before establishing a definitive diagnosis of epilepsy, characterization of the events is a key step. Inpatient video-EEG monitoring is regularly successful but may not capture events if they are too infrequent. Figure 2 visualizes the cumulative probability functions for seizure detection as a function of monitoring duration assuming a constant seizure frequency where each day can be conceived as a Bernoulli trial for a seizure occurring. Many patients will have seizure frequencies < 1/wk and are thus unlikely to have a seizure during a standard EMU visit.

3.5 | Seizure localization

When seizures are refractory to medical treatment, surgery is often indicated and has been increasingly used with improving results in the past decades.⁶⁰ Presurgical workup regularly requires the implantation of intracranial electrodes to refine the localization of the seizure onset zone, sometimes in brain areas inaccessible to scalp or subscalp EEG. However, subscalp EEG that includes bilateral electrode coverage would

enable lateralization of seizures. A study of outpatient after inpatient intracranial EEG monitoring in 82 patients with mesial temporal lobe epilepsy of unknown laterality reclassified 16 (20%) as having unilateral or bilateral onset, which can help evaluate candidates for epilepsy surgery.^{23,24}

Subscalp EEG that offers broad head electrode coverage could localize to a given cerebral lobe, although studies will be needed to confirm this. Basing surgical decisions on dozens to hundreds of electrographic seizures instead of a handful typically collected in hospital is a promising possibility for the future. Subscalp EEG will improve the continuum between optimization of medical treatment and presurgical planning, and represents a bridge partially mitigating both the critical lack of information in outpatient epileptology and the somewhat artificial conditions imposed in the EMU.¹¹

3.6 | Seizure alarming

A majority of patients and caregivers want some form of seizure monitoring, either at night only or 24/7, to feel more safe and less stigmatized.⁶¹ This is where subscalp EEG is most likely to improve the everyday life of a person with epilepsy. A large study on quality of life (QoL) in epilepsy describes problems in terms of lower self-esteem, higher levels of anxiety and depression, social isolation, stigmatization, risk of sudden unexpected death in epilepsy (SUDEP), and higher rate of unemployment.⁶² Injuries (burns, head and dental injuries) increase with higher seizure frequency. Feelings of stigmatization were common, and 48% worried about epilepsy some or much of the time. Hopefully, a reliable online alarm can alleviate such issues.

SUDEP is a major cause of anxiety and is one of the primary motivations some people with epilepsy have for wanting a seizure alarm. Death following a seizure may be preceded by a critical interval, where an intervention could potentially save lives.⁶³ Because GTCS are the main risk factor for SUDEP,⁶³ the motivation for seizure alarming for SUDEP prevention may be weaker for focal non-tonic-clonic seizures. For a subscalp device to be relevant for SUDEP prevention, it needs to provide at least equivalent performance to wearables, or it could be part of a multimodal system that is more robust. It could also be used to assess whether the risk of SUDEP changes over time for a certain patient by estimating changes in the postictal EEG, although this has to be shown in a clinical trial.^{64–66}

3.7 | Seizure forecasting

When patients are asked directly about the impact of seizure unpredictability, 66%–68% consider it an important or very important aspect.⁶⁷ Developing systems that can predict the

occurrence of a future seizure event with sufficient time to act would be a game changer. Instead of a binary output, the prediction could be expressed as elevated seizure risk, referred to as seizure forecasting. One successful demonstration of seizure forecasting used intracranial EEG recordings to provide visual feedback to patients minutes in advance of seizures.⁶⁸ Much effort has been put into developing solutions for seizure prediction combining intracranial EEG dataset and online competitions reaching classification accuracies of 81%.⁶⁹

However, as intracranial recordings are unlikely to become widespread due to their invasiveness, it will be relevant to test whether good forecasting performance can be achieved on subscalp recordings. Although no prospective study with good forecasting results on extracranial EEG has yet been carried out, the authors are aware of several ongoing studies that hopefully will shed new light on predictability when ultra-long-term recordings are available. Such systems should always be trained and tested on at least several months of labeled data to cover natural physiological variation⁷⁰ and circadian and multidien cycles in epilepsy.²²

3.8 | Using subscalp EEG in the future

Ultra-long-term monitoring can be used both before and after establishing a diagnosis of epilepsy. Long monitoring durations are necessary to detect rare paroxysmal events, as shown in Figure 2. Routinely used solutions of drug tapering, sleep deprivation, and other provocations may in some cases induce events that differ from spontaneous seizures and cloud the interpretation. Therefore, an outpatient-based solution may under these circumstances outperform the EMU. Currently, clinicians will estimate the underlying seizure frequency before referring a patient to the EMU, but if ultra-long-term EEG monitoring is an option, a probability plot as in Figure 2 could be informative when deciding the optimal diagnostic strategy. Furthermore, having a subscalp EEG implant does not prohibit an EMU stay for full video-EEG characterization; on the contrary, given that multidien cycles of seizures are highly prevalent among epilepsy patients,²² the hospital stay could be timed to take place during a period of high likelihood of seizures.¹¹

We envisage a toolkit, whereby subscalp devices for ultra-long-term EEG monitoring can help detect focal or generalized seizures, and non-EEG modalities (EMG, ECG, others) could be “added on” to the setup depending on the specific circumstances. Furthermore, as a relationship between sleep quality/duration and seizure risk has been suggested, the ability to record objective sleep quality and seizures is critical to understanding whether strategies to improve sleep can help seizure control. One study has even shown that two-channel subscalp EEG is sufficient to do robust sleep staging.^{71,72}

4 | READINESS FOR SUBSCALP DEVICES

As no published studies have dealt with the usability of subscalp devices, we must look into the readiness for wearables, scalp EEG, and intracranial EEG.

4.1 | Neurologist readiness

In a survey of 21 neurologists,⁷³ 16 agreed that current ambulatory recordings are diagnostically useful over traditional inpatient recordings, and 18 agreed that there is a further need for wearable EEG devices. Although the questionnaire addresses standard ambulatory EEG, it does give a good indication that there is an unmet need that exceeds the 30-minute routine EEG and 1- to 3-week EMU stay.

Surveys of medical doctors' views on the usefulness of seizure detection devices found that most considered alarms with major motor seizures and seizures associated with fall important, and 53% gave a 4 or 5 on a 0-5 scale of necessity for alarms for impaired awareness during focal seizure and absences.⁶¹

4.2 | Patient readiness

Patients have heterogeneous expectations for the seizure tracking device's performance but describe desirable features in medication reminders, water-proof design, real-time data analysis, improved diagnostics, and seizure management.⁷⁴ Surveys suggest that patients would accept devices for seizure registrations provided that they have only a small negative effect on daily life,⁷⁵ but patients are concerned about appearance and visibility of sensors, so concealed sensors could help increase user acceptance.¹⁵ Subscalp sensors are concealed but may use an external device for power and/or data storage that can be hidden under the user's clothing. The majority (82%) of surveyed patients expected a seizure detection sensitivity of 90% or better.⁶¹

When asking the patients whether they would agree to wear a device on a daily basis, the participants saw the possible benefits for improved treatment effect and valued this benefit more than the possible inconvenience of wearing a sensor.¹⁵ Most (90%) would prefer the size of a wristwatch or smaller. Obviously, acceptance will vary on an individual basis and depend on the tradeoff between perceived benefit and the sum of inconveniences and potential side effects. It must be kept in mind that the questionnaires mentioned deal in hypotheticals regarding implantable devices, and what patients might imagine when posed such questions may not accurately reflect their reactions toward the real devices detailed in this review. The implantable cardiac loop recorder

is well accepted, and so it seems likely that with sufficient benefit for the recipient, implantable subscalp EEG devices will also be well accepted.

Some surveys suggest that up to 45.8% of patients think documentation of seizures is either an "important" or an "essential" feature in a long-term seizure detection system.⁷⁵ Seizure alarming can help to reduce anxiety and assist autonomy; 60.6% of caregivers found that the seizure alarm gave them more freedom, and 30.3% believed that it gave the patients more autonomy.⁷⁶

5 | CHALLENGES AND LIMITATIONS OF SUBSCALP EEG RECORDERS

In this section, we outline proposed objectives in future trials, considerations about low spatial resolution, logistical considerations relating to implantation, data management, and safety.

5.1 | Future trials

Future trials involving ultra-long-term monitoring in epilepsy using subscalp EEG will be required to explore the value proposition of the technology. Although the first safety and feasibility studies have been completed, evidence of clinical usefulness of ultra-long-term EEG recordings is not available at the current stage of development, although multiple studies are in preparation or have commenced.

Development of seizure detection algorithms should follow the standards for reporting diagnostic accuracy proposed in Beniczky and Ryvlin⁷⁷ or Cohen.⁷⁸ We should be moving from small sample sizes and repeated training on retrospective data to prospective trials with larger samples and pre-defined thresholds for the algorithm's detection. It should be clear whether the goal of the trial is seizure alarming or counting. Detection of interictal abnormalities should also adhere to published standards.⁴

Trials on seizure detection devices focus on reliable and accurate seizure counting, which rapidly raises the question of the clinical relevance of the many electrographic seizures typically recorded with ultra-long-term EEG. This is an opportunity to improve the quality of how seizures are defined, although the question is not trivial.⁵² More advanced trials aimed at optimizing medical management, increasing the ability to identify a change in seizure frequency, or informing epilepsy surgery will be necessary after this first step is achieved. Using the classical patient-reported outcomes for such trials (including seizure self-report) would defy the purpose. Other impacts could be quantified in terms of QoL scores, changes in level of disability, number of accidents,

and mortality, or simply whether the neurologist found a treatment improvement or was aided in reaching his therapeutic decisions.

Without a full understanding of the real seizure burden, outcomes of medication trials are often set for failure, prolonging patients suffering. Simulations based on self-reported seizure events in the SeizureTracker database have investigated factors that can reduce costs of randomized clinical trials on AED efficacy without lowering statistical power, but did not attempt to incorporate seizure event uncertainty directly into the model.⁷⁹ Simulations could be useful in clarifying the impact of objective versus subjective seizure counts in epilepsy for randomized controlled trials on AEDs in advance of real data having been accumulated, which will take many years.

5.2 | Considerations regarding reduced spatial resolution

One disadvantage of most suggested subscalp devices except one compared to standard scalp EEG is reduced spatial resolution. For focal abnormalities, this can result in lower sensitivity compared to standard scalp EEG, but strategically selecting the location of the subscalp electrodes (eg, guided by abnormality seen on standard EEG or magnetic resonance imaging) might be useful to inform placement in individual cases. Spikes in the interictal EEG might inform implantation strategy, but unilateral implantation will likely miss seizures confined to the contralateral hemisphere, precluding a discovery of bilateral seizure onset in such cases. In the absence of interictal spikes and lateralizing semiology from the patient history, but where a strong suspicion of epilepsy is present, a bilateral implantation strategy could be considered. One development has shown that it is possible to place electrodes according to the 10-20 system in the subscalp space with minimally invasive surgery, although it is done under general anesthesia. Importantly, a major limitation of subscalp EEG as compared to intracranial EEG is that it cannot monitor deep structures of the brain and has in that sense the same “field of view” as scalp EEG.

6 | CONCLUSIONS

Subscalp EEG recording is an emergent technology. Studies comparing subscalp recordings with scalp EEG are favorable and show that seizures can be documented electrographically. Different devices are being developed to offer a range of subscalp electrode coverage, some with minimally invasive implantation of just a few electrodes under local anesthesia,

others increasing coverage to the full head with general anesthesia. Some devices are fit for seizure counting, whereas others aim at localization.

The true value of ultra-long-term EEG has yet to be established. It could give novel insights into brain function and is likely to open new avenues for biomarker discovery, personalized treatment, and population analytics, especially when combined with other complementary information such as movement and heart rate. Only when data have been collected over long periods of time will the true value of algorithm development for seizure prediction in patients be apparent.

Adoption of subscalp EEG for ultra-long-term monitoring in epilepsy will cause a shift away from subjective seizure reporting in favor of objective seizure counting, a long-awaited change. This could have a broad impact on the daily management of epilepsy and place patients at the center of management of the disorder.

For clinical science, the technology will also facilitate the collection of otherwise very rare ultra-long-term EEG recordings that could not only provide novel insights into epilepsy and other brain diseases but also provide high temporal resolution of physiological short- and long-term rhythms over time.

ACKNOWLEDGMENTS

M.P.R. is funded in part by MRC Centre for Neurodevelopmental Disorders (MR/N026063/1), the National Institute for Health Research Biomedical Research Centre at South London and Maudsley National Health Service Foundation Trust and the Epilepsy Foundation. M.C. is funded by the Epilepsy Foundation and National Health and Medical Research Council. T.W.K. is funded in part by the health science foundations of Region of Zealand and Region of Southern Denmark, as well as Innovation Fund Denmark.

CONFLICT OF INTEREST

J.D.-H. is a full-time employee at UNEEG medical, a company developing and producing a subscalp EEG device. M.B. is a part-time employee at Wyss Center for Bio and Neuroengineering, a not-for-profit foundation, and coinventor on an international patent application under the Patent Cooperation Treaty number 62665486 entitled “Neural Interface System.” M.P.R. holds research funding from Medical Research Council, National Institute for Health Research, Wellcome, Epilepsy Research UK, Epilepsy Foundation of America, European Commission, and Canadian Institutes of Health Research. He is UK Chief Investigator of a trial sponsored by Xenon Pharma and has research collaborations with UNEEG, UCB, ANT Neuro, J&J, and Seer Medical. He has been an advisory board member for UNEEG medical. He holds patent WO2013182848A1. M.C. is CMO at Epi-Minder, as

well as CMO at SEER Medical. G.K. is Chief Technology Officer at the Wyss Center for Bio and Neuroengineering, an independent, nonprofit research and development organization developing a subscalp EEG device. J.M.H. consults for Epi-Minder, a company developing a subscalp EEG device. D.F. is a cofounder of Neuroview Technology and holds equity interests in the company. He also receives salary support for consulting and clinical trial-related activities performed on behalf of the Epilepsy Study Consortium, a nonprofit organization. D.F. receives no personal income for these activities. New York University receives a fixed amount from the Epilepsy Study Consortium toward D.F.'s salary. Within the past year, the Epilepsy Study Consortium received payments for research services performed by D.F. from Adamas, Axcella, Biogen, Crossject, CuroNZ, Engage Pharmaceuticals, Eisai, GW Pharmaceuticals, Pfizer, SK Life Science, Takeda, Xenon, and Zynerba. He has also served as a paid consultant for Eisai. He has received an honorarium from Neuropace. He has received travel support from Medtronic, Eisai, and the Epilepsy Foundation. He receives research support from the Centers for Disease Control and Prevention, The National Institute of Neurological Disorders and Stroke, Epilepsy Foundation, Empatica, EpiTel, UCB, and Neuropace. He serves on the scientific advisory board for Receptor Life Sciences and holds equity interests in the company. J.P. has participated in clinical trials for Eisai, UCB, and Bial; received research grants from Eisai, Medtronic, UCB, and LivaNova; received speaker honoraria from LivaNova, Eisai, Medtronic, Orion Pharma, and UCB; received support for travel to congresses from LivaNova, Eisai, Medtronic, and UCB; and participated in advisory boards for LivaNova, Eisai, Medtronic, UCB, and Pfizer. He is a cofounder of Neuroeventlabs and holds equity interest in the company. He is also medical advisor to Braincare. I.C.Z. consults for UNEEG medical. T.W.K. consults for UNEEG medical. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID

Jonas Duun-Henriksen  <https://orcid.org/0000-0003-1558-8225>

Maxime Baud  <https://orcid.org/0000-0002-8297-7696>

Mark P. Richardson  <https://orcid.org/0000-0001-8925-3140>

Mark Cook  <https://orcid.org/0000-0002-8875-4135>

Daniel Friedman  <https://orcid.org/0000-0003-1068-1797>

Ivan C. Zibrandtsen  <https://orcid.org/0000-0002-0529-0110>

Troels W. Kjaer  <https://orcid.org/0000-0002-2105-6199>

REFERENCES

- Blachut B, Hoppe C, Surges R, Elger C, Helmstaedter C. Subjective seizure counts by epilepsy clinical drug trial participants are not reliable. *Epilepsy Behav.* 2017;67:122–7.
- Elger CE, Hoppe C. Diagnostic challenges in epilepsy: seizure under-reporting and seizure detection. *Lancet Neurol.* 2018;17(3):279–88.
- Ramgopal S, Thome-Souza S, Jackson M, et al. Seizure detection, seizure prediction, and closed-loop warning systems in epilepsy. *Epilepsy Behav.* 2014;37:291–307.
- Casson AJ, Luna E, Rodriguez-Villegas E. Performance metrics for the accurate characterisation of interictal spike detection algorithms. *J Neurosci Methods.* 2009;177(2):479–87.
- Bateson AD, Baseler HA, Paulson KS, Ahmed F, Asghar AUR. Categorisation of mobile EEG: a researcher's perspective. *BioMed Res Int.* 2017;2017:1–15.
- Casson AJ. Wearable EEG and beyond. *Biomed Eng Lett.* 2019;9(1):53–71.
- Van de Vel A, Cuppens K, Bonroy B, et al. Non-EEG seizure detection systems and potential SUDEP prevention: state of the art: review and update. *Seizure.* 2016;41:141–53.
- Bidwell J, Khuwatsamrit T, Askew B, Ehrenberg JA, Helmers S. Seizure reporting technologies for epilepsy treatment: a review of clinical information needs and supporting technologies. *Seizure.* 2015;32:109–17.
- Jory C, Shankar R, Coker D, McLean B, Hanna J, Newman C. Safe and sound? A systematic literature review of seizure detection methods for personal use. *Seizure.* 2016;36:4–15.
- Leijten FSS, Dutch TeleEpilepsy Consortium. Multimodal seizure detection: a review. *Epilepsia.* 2018;59(Suppl 1):42–7.
- Baud MO, Rao VR. Gauging seizure risk. *Neurology.* 2018;91(21):967–73.
- Khan S, Nobili L, Khatami R, et al. Circadian rhythm and epilepsy. *Lancet Neurol.* 2018;17(12):1098–108.
- Krahn AD, Klein GJ, Yee R, Skanes AC. The use of monitoring strategies in patients with unexplained syncope—role of the external and implantable loop recorder. *Clin Auton Res.* 2004;14(Suppl 1):55–61.
- Krahn AD, Klein GJ, Skanes AC, Yee R. Insertable loop recorder use for detection of intermittent arrhythmias. *Pacing Clin Electrophysiol.* 2004;27(5):657–64.
- Bruno E, Simblett S, Lang A, et al. Wearable technology in epilepsy: the views of patients, caregivers, and healthcare professionals. *Epilepsy Behav.* 2018;85:141–9.
- Tatum WO, Rubboli G, Kaplan PW, et al. Clinical utility of EEG in diagnosing and monitoring epilepsy in adults. *Clin Neurophysiol.* 2018;129(5):1056–82.
- Goodwin E, Kandler RH, Alix JJP. The value of home video with ambulatory EEG: a prospective service review. *Seizure.* 2014;23(6):480–2.
- Kandler R, Ponnusamy A, Wragg C. Video ambulatory EEG: a good alternative to inpatient video telemetry? *Seizure.* 2017;47:66–70.
- Wong CH, Birkett J, Byth K, et al. Risk factors for complications during intracranial electrode recording in presurgical evaluation of drug resistant partial epilepsy. *Acta Neurochir.* 2009;151(1):37–50.
- Chan AY, Knowlton RC, Chang EF, Rao VR. Seizure localization by chronic ambulatory electrocorticography. *Clin Neurophysiol Pract.* 2018;3:174–6.
- Karoly PJ, Freestone DR, Boston R, et al. Interictal spikes and epileptic seizures: their relationship and underlying rhythmicity. *Brain.* 2016;139(4):1066–78.
- Baud MO, Kleen JK, Mirro EA, et al. Multi-day rhythms modulate seizure risk in epilepsy. *Nat Commun.* 2018;9(1):1–10.

23. King-Stephens D, Mirro E, Weber PB, et al. Lateralization of mesial temporal lobe epilepsy with chronic ambulatory electrocorticography. *Epilepsia*. 2015;56(6):959–67.
24. Hirsch LJ, Mirro EA, Salanova V, et al. Mesial temporal resection following long-term ambulatory intracranial EEG monitoring with a direct brain-responsive neurostimulation system. *Epilepsia*. 2020;61(3):408–20.
25. Wendel K, Väisänen J, Seemann G, Hyttinen J, Malmivuo J. The influence of age and skull conductivity on surface and subdermal bipolar EEG leads. *Comput Intell Neurosci*. 2010;2010:397272.
26. Duun-Henriksen J, Kjaer T, Sørensen J, Juhl C. Ultra-long term subcutaneous recording system for EEG surveillance. 15th Eur Congr Clin Neurophysiol. 2015;127(3):e104–5.
27. Young GB, Ives JR, Chapman MG, Mirsattari SM. A comparison of subdermal wire electrodes with collodion-applied disk electrodes in long-term EEG recordings in ICU. *Clin Neurophysiol*. 2006;117(6):1376–9.
28. Mendes MR, Subramaniam NP, Wendel-Mitoraj K. Evaluating the electrode measurement sensitivity of subdermal electroencephalography electrodes. In: 2015 7th International IEEE/EMBS Conference on Neural Engineering (NER). Montpellier, France: IEEE; 2015:1092–5.
29. Duun-Henriksen J, Kjaer TW, Looney D, et al. EEG signal quality of a subcutaneous recording system compared to standard surface electrodes. *J Sens*. 2015;2015:1–9.
30. Islam MK, Rastegarnia A, Yang Z. Methods for artifact detection and removal from scalp EEG: a review. *Neurophysiol Clin*. 2016;46(4–5):287–305.
31. Liu Q, Liu A, Zhang X, Chen X, Qian R, Chen X. Removal of EMG artifacts from multichannel EEG signals using combined singular spectrum analysis and canonical correlation analysis. *J Healthc Eng*. 2019;2019:1–13.
32. Weisdorf S, Gangstad SW, Duun-Henriksen J, Mosholt KSS, Kjaer TW. High similarity between EEG from subcutaneous and proximate scalp electrodes in patients with temporal lobe epilepsy. *J Neurophysiol*. 2018;120(3):1451–60.
33. Weisdorf S, Duun-Henriksen J, Kjeldsen MJ, Poulsen FR, Gangstad SW, Kjaer TW. Ultra-long-term subcutaneous home monitoring of epilepsy—490 days of EEG from nine patients. *Epilepsia*. 2019;60(3):2204–14.
34. 24/7 EEG™ SubQ. Available at: <https://www.uneeg.com/en/epilepsy/products/subq>. Accessed June 16, 2020.
35. EASEE® electrode. Available at: <https://precisis.de/en/technology/subcutaneous-electrode>. Accessed June 16, 2020.
36. Epios™. Available at: <https://www.wysscenter.ch/advances/epios-brain-monitoring>. Accessed June 16, 2020.
37. Neuroview Technology. Available at: <https://neuroviewtech.com/>. Accessed June 16, 2020.
38. Jochum T, Engdahl S, Kolls BJ, Wolf P. Implanted electrodes for multi-month EEG. In: 2014 36th Annu Int Conf IEEE Eng Med Biol Soc EMBC. Chicago, IL: IEEE; 2014:6543–8.
39. Ahmed Z, Reddy J, Deshpande K, et al. Flexible ultra-resolution subdermal EEG probes. In: 2018 IEEE Biomedical Circuits and Systems Conference (BioCAS). Cleveland, OH, USA: IEEE; 2018:1–4.
40. Do Valle BG, Cash SS, Sodini CG. Low-power, 8-channel EEG recorder and seizure detector ASIC for a subdermal implantable system. *IEEE Trans Biomed Circuits Syst*. 2016;10(6):1058–67.
41. Xu J, Wang B, McLaughlin B, Schachther S, Yang Z. An integrated sub-scalp EEG sensor for diagnosis in epilepsy. In: IEEE Biomed Circuits Syst Conf Eng Healthy Minds Able Bodies BioCAS 2015—Proc. Atlanta, GA: IEEE; 2015:1–4.
42. van Westrhenen A, De Cooman T, Lazerion RHC, Van Huffel S, Thijs RD. Ictal autonomic changes as a tool for seizure detection: a systematic review. *Clin Auton Res*. 2019;29(2):161–81.
43. Poh M-Z, Swenson NC, Picard RW. A wearable sensor for unobtrusive, long-term assessment of electrodermal activity. *IEEE Trans Biomed Eng*. 2010;57(5):1243–52.
44. Meyer S, Strittmatter M. Autonomic changes with seizures correlate with postictal EEG suppression. *Neurology*. 2013;80(16):1538–9.
45. Beniczky S, Neufeld M, Diehl B, et al. Testing patients during seizures: a European consensus procedure developed by a joint taskforce of the ILAE—Commission on European Affairs and the European Epilepsy Monitoring Unit Association. *Epilepsia*. 2016;57(9):1363–8.
46. Maslen H, Cheeran B, Pugh J, et al. Unexpected complications of novel deep brain stimulation treatments: ethical issues and clinical recommendations: novel deep brain stimulation treatments. *Neuromodulat Technol Neural Interface*. 2018;21(2):135–43.
47. Umemura A, Oyama G, Shimo Y, et al. Current topics in deep brain stimulation for Parkinson disease. *Neurol Med Chir*. 2016;56(10):613–25.
48. Robbins MS, Lipton RB. Transcutaneous and percutaneous neurostimulation for headache disorders. *Headache J Head Face Pain*. 2017;57:4–13.
49. Miller S, Sinclair AJ, Davies B, Matharu M. Neurostimulation in the treatment of primary headaches. *Pract Neurol*. 2016;16(5):362–75.
50. Martz GU, Hucek C, Quigg M. Sixty day continuous use of subdermal wire electrodes for EEG monitoring during treatment of status epilepticus. *Neurocrit Care*. 2009;11(2):223–7.
51. Benbadis S. The differential diagnosis of epilepsy: a critical review. *Epilepsy Behav*. 2009;15(1):15–21.
52. Karoly P, Goldenholz DM, Cook M. Are the days of counting seizures numbered? *Curr Opin Neurol*. 2018;31(2):162–8.
53. Bell B, Lin JJ, Seidenberg M, Hermann B. The neurobiology of cognitive disorders in temporal lobe epilepsy. *Nat Rev Neurol*. 2011;7(3):154–64.
54. Sutula TP, Hagen J, Pitkänen A. Do epileptic seizures damage the brain? *Curr Opin Neurol*. 2003;16(2):189–95.
55. Fisher RS, Blum DE, DiVentura B, et al. Seizure diaries for clinical research and practice: limitations and future prospects. *Epilepsy Behav*. 2012;24(3):304–10.
56. Hoppe C, Poepel A, Elger CE. Epilepsy: accuracy of patient seizure counts. *Arch Neurol*. 2007;64(11):1595–9.
57. Bruno E, Viana PF, Sperling MR, Richardson MP. Seizure detection at home: do devices on the market match the needs of people living with epilepsy and their caregivers? *Epilepsia*. 2020. <http://dx.doi.org/10.1111/epi.16521>.
58. Weisdorf S, Zibrandtsen IC, Kjaer TW. Subcutaneous EEG monitoring reveals AED response and breakthrough seizures. *Case Rep Neurol Med*. 2020;2020:1–6.
59. Karoly PJ, Goldenholz DM, Freestone DR, et al. Circadian and circaseptan rhythms in human epilepsy: a retrospective cohort study. *Lancet Neurol*. 2018;17(11):977–85.
60. Baud MO, Perneger T, Rácz A, et al. European trends in epilepsy surgery. *Neurology*. 2018;91(2):e96–106.
61. Van de Vel A, Smets K, Wouters K, Ceulemans B. Automated non-EEG based seizure detection: do users have a say? *Epilepsy Behav*. 2016;62:121–8.
62. Taylor RS, Sander JW, Taylor RJ, Baker GA. Predictors of health-related quality of life and costs in adults with epilepsy: a systematic review. *Epilepsia*. 2011;52(12):2168–80.

63. Ryvlin P, Nashef L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. *Lancet Neurol.* 2013;12(10):966–77.
64. Pottkämper JCM, Hofmeijer J, van Waarde JA, van Putten MJAM. The postictal state—what do we know? *Epilepsia.* 2020;61:1045–61.
65. Carlson C. Generalized postictal EEG background suppression: a marker of SUDEP risk: postictal EEG suppression and SUDEP. *Epilepsy Curr.* 2011;11(3):86–7.
66. Arbune AA, Conradsen I, Cardenas DP, et al. Ictal quantitative surface electromyography correlates with postictal EEG suppression. *Neurology.* 2020;94(24):e2567–76.
67. Schulze-Bonhage A, Sales F, Wagner K, et al. Views of patients with epilepsy on seizure prediction devices. *Epilepsy Behav.* 2010;18(4):388–96.
68. Cook MJ, O'Brien TJ, Berkovic SF, et al. Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study. *Lancet Neurol.* 2013;12(6):563–71.
69. Kuhlmann L, Lehnertz K, Richardson MP, Schelter B, Zaveri HP. Seizure prediction—ready for a new era. *Nat Rev Neurol.* 2018;14(10):618–30.
70. Mormann F, Andrzejak RG, Elger CE, Lehnertz K. Seizure prediction: the long and winding road. *Brain J Neurol.* 2007;130(Pt 2):314–33.
71. Rossi KC, Joe J, Makhija M, Goldenholz DM. Insufficient sleep, electroencephalogram activation, and seizure risk: re-evaluating the evidence. *Ann Neurol.* 2020;87(6):798–806.
72. Gangstad SW, Mikkelsen KB, Kidmose P, et al. Automatic sleep stage classification based on subcutaneous EEG in patients with epilepsy. *Biomed Eng Online.* 2019;18(1):106.
73. Casson AJ, Yates DC, Smith SJM, Duncan JS, Rodriguez-Villegas E. Wearable electroencephalography. *IEEE Eng Med Biol Mag.* 2010;29(3):44–56.
74. Johansson D, Malmgren K, Alt MM. Wearable sensors for clinical applications in epilepsy, Parkinson's disease, and stroke: a mixed-methods systematic review. *J Neurol.* 2018;265(8):1740–52.
75. Hoppe C, Feldmann M, Blachut B, Surges R, Elger CE, Helmstaedter C. Novel techniques for automated seizure registration: patients' wants and needs. *Epilepsy Behav.* 2015;52(Pt A):1–7.
76. Arends J, Thijs RD, Gutter T, et al. Multimodal nocturnal seizure detection in a residential care setting: a long-term prospective trial. *Neurology.* 2018;91(21):e2010–9.
77. Beniczky S, Ryvlin P. Standards for testing and clinical validation of seizure detection devices. *Epilepsia.* 2018;59:9–13.
78. Cohen JF, Korevaar DA, Altman DG, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. *BMJ Open.* 2016;6(11):e012799.
79. Goldenholz DM, Tharayil J, Moss R, Myers E, Theodore WH. Monte Carlo simulations of randomized clinical trials in epilepsy. *Ann Clin Transl Neurol.* 2017;4(8):544–52.

How to cite this article: Duun-Henriksen J, Baud M, Richardson MP, et al. A new era in electroencephalographic monitoring? Subscalp devices for ultra-long-term recordings. *Epilepsia.* 2020;61:1805–1817. <https://doi.org/10.1111/epi.16630>